

Claims

1. A process for the preparation of multiple cross-linked derivatives of hyaluronic acid, which process comprises covalently cross-linking HA via two or more different functional groups, wherein said cross-linking is effected by contacting HA with one or more chemical cross-linking agents so as to form two or more chemically distinct cross-links, between said HA molecules
2. A process according to claim 1 wherein the functional groups are selected from hydroxyl, carboxyl and amino.
3. A process according to claim 1 or claim 2 wherein the crosslinking is effected by means of two or more different bonds selected from ether, ester, sulfone, amine, imino and amide bonds.
4. A process according to any of claims 1 to 3 wherein the cross-linking agent is selected from formaldehyde, glutaraldehyde, divinyl sulfone, a polyanhydride, a polyaldehyde, a polyhydric alcohol, carbodiimide, epichlorohydrin, ethylene glycol diglycidylether, butanediol diglycidylether, polyglycerol polyglycidylether, polyethylene glycol diglycidylether, polypropylene glycol diglycidylether, or a bis- or poly-epoxy cross-linker.
5. A process according to any of claims 1 to 4 wherein an ether bond is formed using a crosslinking agent selected from bis and poly epoxides under alkaline conditions.
6. A process according to any of claims 1 to 4 wherein an ester bond is formed using a crosslinking agent selected from bis and poly epoxides under acidic conditions.
7. A process according to claim 5 or claim 6 wherein the crosslinker is selected from 1,2,3,4-diepoxybutane and 1,2,7,8-diepoxyoctane.
8. A process according to any of claims 1 to 4 wherein an ether bond is formed using a glutaraldehyde cross-linking agent under acidic conditions.

Sub 9.
Q2 cont

9. A process according to any of claims 1 to 8 wherein the crosslinking of each type of functional group is effected sequentially.

10. A process according to claim 9 which comprises cross-linking HA via a first functional group and subsequently further cross-linking the product via a second functional group, wherein said first and second functional groups represent different chemical entities.

Sub 13.
Q3

11. A process according to claim 9 or claim 10 wherein HA is first cross-linked via the hydroxyl groups by formation of ether bonds and subsequently cross-linked via the carboxyl groups by formation of ester bonds.

Sub 14.
Q4

12. A process according to any of claims 1 to 8 wherein the crosslinking of each type of functional group is effected simultaneously.

Sub 15.
Q5

13. A process according to any of claims 1 to 12 for preparing double crosslinked HA.

14. A process according to claim 13 which comprises:
(a) cross-linking HA via a first functional group and
(b) subsequently further cross-linking the product of (a) via a second functional group, wherein said first and second functional groups represent different chemical entities.

Sub 16.
Q6

15. Multiple cross-linked HA obtainable by a process according to any of claims 1 to 14.

16. HA cross-linked to a further molecule of HA wherein the HA is crosslinked by at least two different types of bond.

Sub 17.
Q7

17. Cross-linked HA according to claim 15 or claim 16 wherein the crosslinking bonds are selected from two or more of ether, ester, sulfone, amine, imino and amide bonds.

Sub 18.
Q8

18. Multiple cross-linked HA according to any of claims 15 to 17 in the form of a film.

Sub 19.
Q9

19. Multiple cross-linked HA according to any of claims 15 to 17 in the form of a gel.

Sub
a10 20. HA according to any of claims 15 to 19 which is double cross linked HA.

Sub
a11 21. A product comprising ~~multiple~~³ cross-linked HA according to any of claims 15 to 20.

a 22. The use of HA according to any of claims 15 to 20 in the preparation of a product for pharmaceutical, cosmetic or medical use.

23. The use of HA according to any of claims 15 to 20 or a product according to claim 21 in medicine or surgery.